PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 December 1998 (15.12.98)	
International application No. PCT/GB98/01318	**Applicant's or agent's file reference** IMPW/18999PC
International filing date (day/month/year) 07 May 1998 (07.05.98)	**Priority date** (day/month/year) 10 May 1997 (10.05.97)
Applicant GHERARDI, Ermanno et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   20 November 1998 (20.11.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

J. Leitao

Telephone No.: (41-22) 338.83.38

P[redacted]NT COOPERATION TR[redacted]Y

PCT

09/423516

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
IMPW/18999PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 98/ 01318	07/05/1998	10/05/1997
Applicant		
IMPERIAL CANCER RESEARCH TECHNOLOGY LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [X] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [X] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   HGF POLYPEPTIDES AND THEIR USE IN THERAPY

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. 1
   - [X] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/01318

Box I Observations where certain claims were found unsearchabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (3,22) - complete; (1-2, 5-21, 24-37) partial

A variant HGF with reduced heparan sulphate binding but still capable of binding its cognate receptor, wherein at least amino acid R73 has been replaced by an amino acid with no charge or negative charge.

Said variant, in which amino acids R76 and either K78 or R93 have also been mutated. Said variants, further comprising mutations in the region spanning amino acids 493-496 conferring resistance to proteolytic cleavage.

Corresponding polynucleotides, vectors and host cells. Uses of said variant HGF molecules in medicine.

2. Claims: (4,23) - complete; (1-2, 5-21, 24-37) - partial

A variant HGF with reduced heparan sulphate binding but still capable of binding its cognate receptor, wherein at least amino acid R76 has been replaced by an amino acid with no charge or negative charge.

Said variant, in which amino acids R73 and either K78 or R93 have also been mutated. Said variants, further comprising mutations in the region spanning amino acids 493-496 conferring resistance to proteolytic cleavage.

Corresponding polynucleotides, vectors and host cells: Uses of said variant HGF molecules in medicine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/01318

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/19 C12N5/10 C07K14/475 A61K38/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 757 994 A (SNOW BRAND MILK PROD CO LTD) 12 February 1997 see abstract see page 3, line 20 - line 37 see page 7 - page 9	1-3, 20-22,37
Y		12-19, 30-36

X	SAKATA H. ET AL.: "Heparin binding and oligomerization of Hepatocyte Growth Factor/Scatter Factor isoforms" J. BIOL. CHEM., vol. 272, no. 14, 4 April 1997, pages 9457-9463, XP002074885 see the whole document	1,2,4, 20,21, 23,37

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1998	03/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 23541 A (LOKKER NATHALIE A ;GENENTECH INC (US); GODOWSKI PAUL J (US); MARK) 25 November 1993 cited in the application see example 7 see tables 1-3 see claims 1-55	12-19, 30-36
A	MIZUNO K. ET AL.: "Hairpin loop and second Kringle domain are essential sites for heparin binding and biological activity of Hepatocyte Growth Factor" J. BIOL. CHEM., vol. 269, no. 2, 14 January 1994, pages 1131-1136, XP002074886 cited in the application see the whole document	1-37
P,X	HARTMANN G. ET AL.: "Engineered mutants of HGF/SF with reduced binding to heparan sulphate proteoglycans, decreased clearance and enhanced activity in vivo." CURRENT BIOLOGY, vol. 8, no. 3, - 29 January 1998 pages 125-134, XP002074628 see the whole document	1-14, 25-36

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/01318

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0757994 A	12-02-1997	AU 4355196 A	19-07-1996
		FI 963313 A	26-08-1996
		NO 963552 A	28-10-1996
		CA 2183856 A	28-06-1996
		HU 75236 A	28-04-1997
		WO 9620214 A	04-07-1996
		NZ 298142 A	22-08-1997
WO 9323541 A	25-11-1993	US 5316921 A	31-05-1994
		US 5328837 A	12-07-1994
		EP 0642580 A	15-03-1995
		EP 0642585 A	15-03-1995
		JP 7508420 T	21-09-1995
		JP 7508178 T	14-09-1995
		US 5547856 A	20-08-1996
		WO 9323550 A	25-11-1993
		US 5580963 A	03-12-1996
		US 5684136 A	04-11-1997
		US 5763584 A	09-06-1998
		US 5770704 A	23-06-1998

CLAIMS

1. A variant hepatocyte growth factor (HGF) which is substantially incapable of binding a heparan sulphate proteoglycan but which is capable of binding to the HGF receptor wherein a positively-charged amino acid residue in the hairpin loop structure of wild-type HGF has been replaced with an amino acid residue with a negative charge for use in medicine.

2. A variant human hepatocyte growth factor (HGF) according to Claim 1 wherein at least amino acid residue R73 has been replaced by an amino acid residue with a negative charge for use in medicine.

3. A variant human hepatocyte growth factor (HGF) according to Claim 1 or 2 wherein at least amino acid residue R76 has been replaced by an amino acid residue with a negative charge for use in medicine.

4. A variant human hepatocyte growth factor (HGF) according to any one of the preceding claims wherein both amino acid residues R73 and R76 have been replaced independently with an amino acid residue with a negative charge for use in medicine.

5. A variant human hepatocyte growth factor (HGF) comprising amino acid residue replacements R73E and R76E for use in medicine.

6. A variant human hepatocyte growth factor (HGF) comprising amino acid residue replacements R73E, R76E and R93E for use in medicine.

7. A variant human hepatocyte growth factor (HGF) comprising amino acid residue replacements R73E, R76E and K78E for use in medicine.

8. A variant human hepatocyte growth factor (HGF) consisting of human HGF with amino acid replacements R73E and R76E for use in medicine.

9. A variant human hepatocyte growth factor (HGF) consisting of human HGF with amino acid replacements R73E, R76E and R93E for use in medicine.

10. A variant human hepatocyte growth factor (HGF) consisting of human HGF with amino acid replacements R73E, R76E and K78E for use in medicine.

11. A variant hepatocyte growth factor (HGF) according to any one of Claims 1 to 10 which antagonises the action of wild-type HGF for use in medicine.

12. A variant hepatocyte growth factor (HGF) according to Claim 11 wherein the variant HGF further comprises a mutation which confers resistance in the variant HGF to proteolytic cleavage by enzymes capable of *in vivo* conversion of HGF into its two-chain form for use in medicine.

13. A variant human hepatocyte growth factor (HGF) according to Claim 12 which have an amino acid alteration at or adjacent to any of amino acids 493, 494, 495 and 496 of the wild-type human HGF.

14. A pharmaceutical composition comprising a variant hepatocyte growth factor (HGF) as defined in any of the preceding claims and a pharmaceutically acceptable carrier.

15. A method of treating a patient in need of treatment with a hepatocyte growth factor or an antagonist thereof the method comprising administering to the patient an effective amount of a variant HGF as defined in any one of Claims 1 to 13.

16. A method according to Claim 15 wherein the patient has cancer.

17. Use of a variant hepatocyte growth factor (HGF) as defined in any one of Claims 1 to 10 in the manufacture of a medicament for treating a patient in need of treatment with a HGF or an antagonist thereof.

18. Use as defined in Claim 17 wherein the patient has cancer.

19. A variant hepatocyte growth factor (HGF) wherein a positively-charged amino acid residue in the hairpin loop structure of wild-type HGF has been replaced with an amino acid residue with a negative charge provided that the variant HGF is not a variant of human HGF in which the replacements (a) R73E, R76E and R93E

or (b) R73E and R76E or (c) K91E, R93E and K94E have been made.

20. A variant human hepatocyte growth factor (HGF) according to Claim 19 wherein at least amino acid residue R73 has been replaced by an amino acid residue with a negative charge.

21. A variant human hepatocyte growth factor (HGF) according to Claim 19 wherein at least amino acid residue R76 has been replaced by an amino acid residue with a negative charge.

22. A variant human hepatocyte growth factor (HGF) according to any one of Claims 19 to 21 wherein both amino acid residues R73 and R76 have been replaced independently with an amino acid residue with a negative charge.

23. A variant human hepatocyte growth factor (HGF) comprising amino acid residue replacements R73E, R76E and K78E.

24. A variant hepatocyte growth factor (HGF) according to Claim 19 which antagonises the action of wild-type HGF.

25. A variant hepatocyte growth factor (HGF) according to Claim 24 wherein the variant HGF further comprises a mutation which confers resistance in the variant HGF to proteolytic cleavage by enzymes capable of *in vivo* conversion of HGF into its two chain form.

26. A variant human hepatocyte growth factor (HGF) according to Claim 25 which have an amino acid alteration at or adjacent to any of amino acids 493, 494, 495 and 496 of the wild-type human HGF.

27. A polynucleotide encoding a variant hepatocyte growth factor according to any one of Claims 19 to 24.

28. A vector comprising a polynucleotide according to Claim 27.

29. A host cell comprising a polynucleotide or vector according to Claim 27 or 28.

30. A method of producing a variant hepatocyte growth factor (HGF) the method comprising culturing a cell as defined in Claim 29 and isolating the variant HGF therefrom.

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PATENT COOPERATION TREATY

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WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
IMPW/18999PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/01318	07/05/1998	10/05/1997
International Patent Classification (IPC) or national classification and IPC C12N15/19		
Applicant IMPERIAL CANCER RESEARCH TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/11/1998	04.08.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Sprinks, M Telephone No. (+49-89) 2399 8706

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/01318

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-54	as originally filed				

Claims, No.:

1-30	as received on	08/06/1999	with letter of	03/06/1999	

Drawings, sheets:

1/8-8/8	as originally filed				

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☒ the claims, Nos.: 31-37
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed du to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	

2. Citations and explanations

see separate sheet

The following documents (D) are mentioned for the first time in this opinion/report; the numbering will be adhered to in the rest of the procedure:

D1...EP 0 757 994 A
D2...J. Biol. Chem., vol. 272, no. 14, April 1997, pages 9457-9463 (Sakata et al.)
D3...WO 93 23541 A

II) Priority

1) Since the priority documents pertaining to the present application were not available at the time when this opinion/report was established, examination has been based on the assumption that priority is valid for all claims presently on file. However, if at a later date this appears not to be the case, the documents cited as "P" in the international search report may become relevant in the assessment of the claims pursuant to **Article 33 (1) - (3) PCT**.

V) Reasoned statement

Novelty, inventive step and industrial applicability

1) **Claims 1-30** are considered to fulfil the criteria of **Article 33 (2) - (4) PCT** since, in the light of the available prior art, they define what appears to be new, inventive and industrially applicable subject-matter, namely variant HGFs which are substantially incapable of binding a heparan sulphate proteoglycan but which are still capable of binding to the HGF receptor, wherein a positively charged amino acid in the hairpin loop has been replaced with an amino acid with a negative charge.

Any of D1-D3 might be considered to represent the closest prior art. D1 discloses a variant HGF wherein amino acid residue R73 has been replaced by an amino acid residue with no charge - alanine (see page 5, half way down). D2 discloses variant HGFs wherein amino acid residues R76 and K78, or R93 have also been replaced by alanine (see page 9459, second column). D3 discloses variant HGFs wherein amino acid residues R76 and K78 have been replaced by alanine, as well as variant HGFs wherein residues 493-496 have been mutated, leading to

resistance to proteolytic cleavage (see tables 1 and 3). D1-D3 also disclose polynucleotides encoding the variant HGFs referred to above, as well as host-vector expression systems for their production and potential medical uses thereof.

However, in view of the fact that none of these documents disclose or suggest that positively charged residues could be substituted even less conservatively with negatively charged ones and still maintain HGF receptor binding activity, the skilled person (himself being rather conservative in his activities) would have no incentive to try such substitutions with any reasonable expectation of success.

Industrial applicability

2) For the assessment of the subject-matter of present **claims 15 and 16** (as far as *in vivo* methods are concerned) on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. Another consequence of the above is that the wording "for use in therapy" (and equivalents thereof) does not have precisely the same effect on novelty under the **PCT** as it does during European Patent examination.